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RESEARCH REPORT

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Analysis of 17 948 pediatric patients undergoing procedural sedation with a combination of intranasal dexmedetomidine and ketamine

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Summary

Background: Intranasal procedural sedation using dexmedetomidine is well described in the literature. The combination of intranasal dexmedetomidine and ketamine is a novel approach for which there are little data on the rate of successful sedation or adverse events.

Objectives: The aim of this study is to evaluate the rate of successful sedation and adverse events of intranasal procedural sedation using a combination of dexmedetomidine and ketamine for diagnostic examination in children.

Methods: This was a retrospective study and data were collected after ethics approval. A total of 17 948 pediatric patients (7718 females, 10 230 males) in a tertiary hospital in China were evaluated. Patients received a combination of 2 μg kg^{-1} of dexmedetomidine and 1 mg kg^{-1} of ketamine intranasally for procedural sedation. The level of sedation and recovery was assessed by the Modified Observer Assessment of Alertness/Sedation scale and the Modified Aldrete Score.

Results: The rate of intranasal sedation success was 93% (16691/17948), intranasal sedation rescue was 1.8% (322/17948), and intranasal sedation failure was 5.2% (935/17948). Sedation success was defined as successful completed the diagnostic examination and obtained adequate diagnostic-quality images and reports. Intranasal sedation success, rescue and failure were respectively defined as sedation success with intranasal a single dose, additional bolus dose and the need for intravenous (IV) medications/inhalation agents. Median sedation time was 62 min (interquartile range: 55-70 min), median time for onset of sedation was 15 min (interquartile range: 15-20 min), and median sedation recovery time was 45 min (interquartile range: 38-53 min). Incidence of adverse events was low (0.58%; 105/17948), with major and minor adverse event being reported in 0.02% (4/17948) and 0.56% (101/17948) patients, respectively. Postoperative nausea and vomiting was the most common (0.3%; 53/17948) minor adverse event.

Conclusion: Procedural sedation using a combination of intranasal dexmedetomidine and ketamine is associated with acceptable effectiveness and low rates of adverse events.

KEYWORDS
adverse events, dexmedetomidine and ketamine, intranasal

1 | INTRODUCTION

Sedation for precooperative or highly anxious pediatric patients is often required for diagnostic procedures such as electroencephalogram (EEG), magnetic resonance imaging (MRI), electrocardiogram (ECG), computed tomography (CT), and transthoracic echocardiography (TTE).

Ketamine has been used for procedural sedation including by the intranasal route,[1-4] but it has some undesirable side effects — nausea, hypertension, and tachycardia. Dexmedetomidine is useful as a sedative/hypnotic, and offers the advantage of having both sedative and anxiolytic effects, as well as relatively mild analgesic properties and a relatively short elimination half-life of 2 h.[5] Dexmedetomidine has been useful by the intranasal route,[6-10] but has some drawbacks in terms of effectiveness, onset and offset time.

The potential hemodynamic effects of dexmedetomidine include bradycardia and hypotension, especially when larger doses are administered. It has been shown that dexmedetomidine may reduce the incidence of salivation, hypertension, tachycardia and emergence phenomena from ketamine; Ketamine may prevent bradycardia and hypotension of dexmedetomidine. A combination of dexmedetomidine and ketamine can effectively increase the speed of onset of sedation, thereby eliminating the slow onset time when dexmedetomidine is used as the sole agent.[11] Combination of ketamine and dexmedetomidine by the intranasal route has not been widely reported, but is logical because the effects of the drugs are complementary.

We present a large dataset of the use of this combination for diagnostic procedures in an outpatient setting. Our aim was to evaluate the rate of successful sedation and adverse events of intranasal procedural sedation using a combination of dexmedetomidine and ketamine for diagnostic examination in children.

What is already known

- Pediatric patients often require sedation.
- The use of intranasal dexmedetomidine is well described in the literature.

What this article adds

- Procedural sedation using a combination of intranasal dexmedetomidine and ketamine is associated with acceptable effectiveness and low rates of adverse events.

2 | PATIENTS AND METHODS

2.1 | Patient population

This was a retrospective study in which we evaluated outpatient records to identify patients who were sedated using the combination of dexmedetomidine 2 μg kg^{-1} and ketamine 1 mg kg^{-1} by the intranasal route. The protocol was approved by the Institutional Review Board of the Children's Hospital of Chongqing Medical University. We screened outpatient medical records by looking at electronic records from our hospital database to identify all patients using a combination of dexmedetomidine and ketamine as their sedation agents from April 2016 to October 2017.

2.2 | Sedation method

During the study period, our standard procedure included an anesthesiologist evaluated the patient's general condition, history of past illnesses, characteristics of present illness, history of past surgical procedures, allergies, and history of sedation, before deciding on the type of sedation method. Intranasal dexmedetomidine and ketamine were routinely used in our hospital to sedate children, unless there were clear contraindications (eg, allergies to dexmedetomidine or ketamine, renal or hepatic dysfunction, symptomatic airway obstructions, severe cardiac arrhythmias such as II- and III-degree heart block, intracranial hypertension, and anatomical anomaly of the nasal cavity).

After evaluation by the attending anesthesiologist, the patient was closely monitored, and the relevant data were recorded. The attending nursing officer prepared the sedation medicine according to the weight of the patient using a 1 mL tuberculin syringe. The patient's nasal passages were cleaned before intranasal sedation. The undiluted drug with 2 μg kg^{-1} dexmedetomidine and 1 mg kg^{-1} ketamine was administered slowly into both nostrils by the nurse after the patient fasted for at least 1 h (the concentrations of dexmedetomidine and ketamine were 100 mg ml^{-1} and 50 mg ml^{-1}), and then, the alae of the nose was gently massaged to facilitate fluid absorption. All children were encouraged to remain in the supine position for 1-2 min in the arms of their parents in order to maximize drug absorption. Because the skill of administration of intranasal medications may determine the effectiveness of the drug combination, the nurses who administered the drug were trained in a structured program to assure competency. Satisfactory sedation defined as Modified Observer's Assessment of Alertness and Sedation (MOAA/S) score of less than or equal to 3 within 30 min. When a satisfactory sedation effect was achieved, the patient was sent to the examination room by the nurse or anesthetist and children's guardians (American Society of

Anesthesiologists physical status (ASAPS) Class 1-2 patients and ASAPS Class 3 patients with normal cardiopulmonary function were escorted to the examination room by a nurse. ASAPS Class 3 patients with abnormal cardiopulmonary function and ASAPS Class 4 patients were escorted by an anesthetist). In the examination room, the attending physicians monitored the patients breathing and heart rate using a portable monitor. Upon completion of the examination, the attending operators would contact the nurse of the sedation center, then patients were taken back to the sedation center by the nurse. The patients recovered in bed or in the arms of their parents until they were discharged. Parents were encouraged to wake up their children with gentle tactile stimulation or by calling their names. Children were discharged upon attaining a Modified Aldrete Score (MAS) of 9 (for cyanotic congenital heart disease patients, a MAS of 8).

1. Sedation success was defined as successful completed the diagnostic examination and obtained adequate diagnostic-quality images and reports.
2. Intranasal sedation success was defined as sedation success with intranasal a single dose of 2 μg kg^{-1} dexmedetomidine and 1 mg kg^{-1} ketamine; Intranasal sedation rescue was defined as sedation success using intranasal additional bolus dose of 1 μg kg^{-1} dexmedetomidine and 0.5 mg kg^{-1} ketamine; Intranasal sedation failure was defined as the need for intravenous medications/inhalation agents in addition to rescue medications described above.
3. Sedation time was defined as the time from drug administration to discharge from hospital; time for onset of sedation was defined as the time from drug administration to the onset of satisfactory sedation. Sedation recovery time was defined as the time from satisfactory sedation to discharge from hospital.
4. We assessed the incidence of major and minor adverse events as outcome measures. Major adverse events were defined as any one of the following events: (a) emergency airway management (including tracheal intubation, positive pressure ventilation, or placement of another airway device (oropharyngeal airway, nasopharyngeal tube, or laryngeal mask airway)); (b) laryngospasm; (c) cardiac arrhythmias; (d) cardiac arrest; or (e) death.

Minor adverse events include: (a) postoperative nausea and vomiting (PONV) (for PONV, this was scored as follows: no nausea or retching = 0, nausea or retching only = 1, one episode of vomiting = 2, more than one episode of vomiting = 3. For PONV score of >1, we considered it as occurrence of PONV); (b) unexpected changes in heart rate or blood pressure by >20% of the normal, age-adjusted values[12] and requiring pharmacological interventions (in situations where heart rate decreased by >20% of normal age-adjusted values and such changes were not rectified by simple rest or physical stimulation, an injection of atropine of 0.01 mg kg^{-1} (minimum dose: 0.1 mg; maximum dose: 0.5 mg) would be given); (c) blood oxygen saturation (SpO_2) reduction to <90% (for cyanotic congenital heart diseases, reduction of <10% of the baseline value); (d) upper airway obstructions (without airway interventions, and recovered by airway repositioning, supplemental oxygen, and suctioning); (e) delayed awakening, defined as a sedation time of >2 h; or (f) rash.

2.3 | Data collection

We collected information on age, weight, gender, ASAPS, fasting time, successful sedation rate, sedation time, type of examination, primary diagnosis and any adverse events encountered during treatment.

2.4 | Statistical analysis

Descriptive statistics were calculated using counts, frequencies, medians, and interquartile ranges (IRQs) for patient demographics and sedation procedure characteristics. Categorical variables were reported as percentages. The rates were calculated, and 95% confidence intervals (CIs) have been provided. All data analyses were performed using the SPSS statistical software (SPSS Inc. Released 2008. SPSS Statistics for Windows, Version 17.0. Chicago: SPSS Inc).

3 | RESULTS

3.1 | Demographics and sedation characteristics

For the period of April 2016 to October 2017, a total of 17 948 cases were included in our analysis (Figure 1). Demographics and sedation characteristics of the included cases are illustrated in Table 1. The majority of patients who were sedated were <5 years of age, 13 461 were <3 years old (75%), and 2153 were older than 5 years of age (12%). Children who were older than 5 years of age primarily included children who had cerebral palsy and were undergoing an EEG examination. Boys were slightly more prevalent than girls. In total, 15 367 (85.6%) of the sedated patients were assigned ASAPS Class 1 or Class 2 at the time of sedation. Fasting times ranged from 1 to 6 h. Primary diagnoses of the study cases are shown in Figure 2.

3.2 | Diagnostic examinations

The diagnostic examinations applied to the study subjects are summarized in Figure 3. Color Doppler ultrasound, pulmonary function, and EEG accounted for the majority (92.3%) of all diagnostic examinations applied to the study cases.

In our study, a total of 2045 cases received a combination of intranasal dexmedetomidine and ketamine for procedural sedation of EEG from April to December 2016, which included electrode placement for actual recording. We later found that ketamine affected EEG reading and that these patients particularly susceptible to PONV. This observation is consistent with that reported in other published studies.[13-16] After this date, we opted to use intranasal dexmedetomidine for procedural sedation for EEG's.

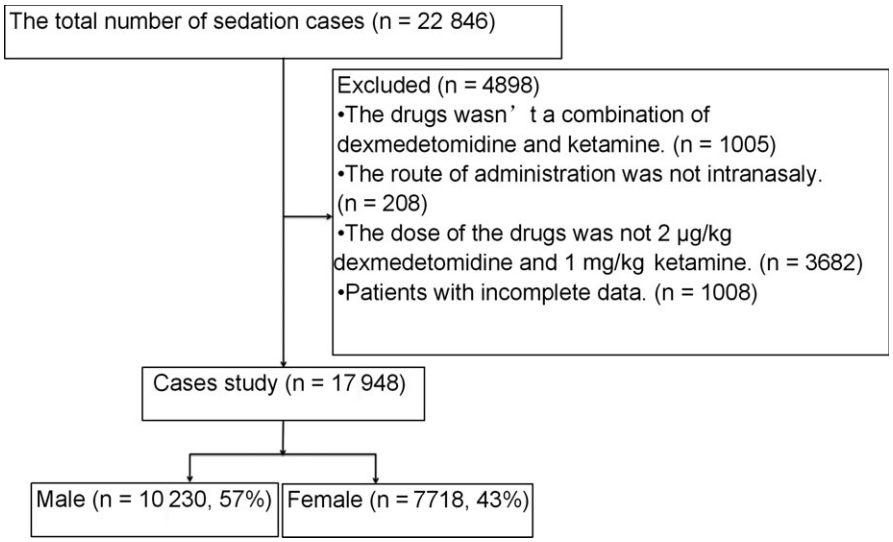

FIGURE 1 CONSORT flow diagram

3.3 | Success rate of intranasal sedation and onset of sedation

The rate of successful intranasal sedation was 93% (n = 16 691), intranasal sedation rescue was 1.8% (n = 322), and intranasal sedation failure was 5.2% (n = 935). Median sedation time was 62 min (IQR: 55-70 min), time for onset of sedation was 15 min (IQR: 15-20 min), and sedation recovery time was 45 min (IQR: 38-53 min). (Table 1).

For MRI cases, intranasal success rate was 60% (n = 430); in the remaining 287 subjects, intranasal sedation rescue was 32.4% (n = 93), and intranasal sedation failure was 67.6% (n = 194). For cases of failed sedation, complete inspection was achieved by inhalation sedation with sevoflurane.

3.4 | Major adverse events

Three patients had to undergo emergency airway management (placement of oropharyngeal airway device) due to upper airway obstructions that were not improved by the adoption of various postures. One was a 2-year-old boy who was diagnosed with Down syndrome and received procedural sedation for TTE. The second patient was a 3-year-old girl with adenoid and tonsillar hypertrophy, who received procedural sedation for a pulmonary function test. The third patient was an overweight (body mass index (BMI): 30.5) 4-year-old boy with adiposity undergoing a pulmonary function test. All of the three children had a MOAA/S score of <3 and showed signs and symptoms of upper airway obstructions, and this was successfully relieved by placing an oral airway. No laryngospasm was reported. Cardiac arrhythmias were reported in a 2-month-old boy with paroxysmal atrial heart rate disorder. Atrial tachycardia occurred 10 min administration of a conventional dose of a combination of dexmedetomidine and ketamine. The heart rate was 250-300 beats min^{-1}. The child was hospitalized immediately and survived without neurologic deficit. No death or cardiac arrest was reported. Major adverse events reported in our study are listed in Table 2.

TABLE 1 Demographics and sedation characteristics

Characteristics	Value
N	17948
Age (months)	21 (10-34)
Weight (kg)	11 (8.5-14)
Gender (M/F)	10230 (57.0)/7718(43)
Sedation time (min)	62 (55-70)
Time for onset of sedation (min)	15 (15-20)
Sedation recovery time (min)	45 (38-53)
ASA PS	
1	8532 (47.5)
2	6835 (38.1)
3	2569 (14.3)
4	12 (0.1)
NPO clear liquids (h)	
<1	142 (0.8)
1-2	9603 (53.5)
2-4	5334 (29.7)
4-6	2671 (14.9)
≥6	198 (1.1)
NPO solids (h)	
1-6	17279 (96.3)
6-8	464 (2.6)
≥8	205 (1.1)

Age, weight, and time expressed as median and interquartile ranges; the other variables expressed as numbers (%).
Sedation time was defined as the time from drug administration to discharge from hospital; time for onset of sedation was defined as the time from drug administration to the onset of satisfactory sedation. Sedation recovery time was defined as the time from satisfactory sedation to discharge from hospital.
Abbreviations: APAPS, American Society of Anesthesiologists physical status; NPO, nil per os.

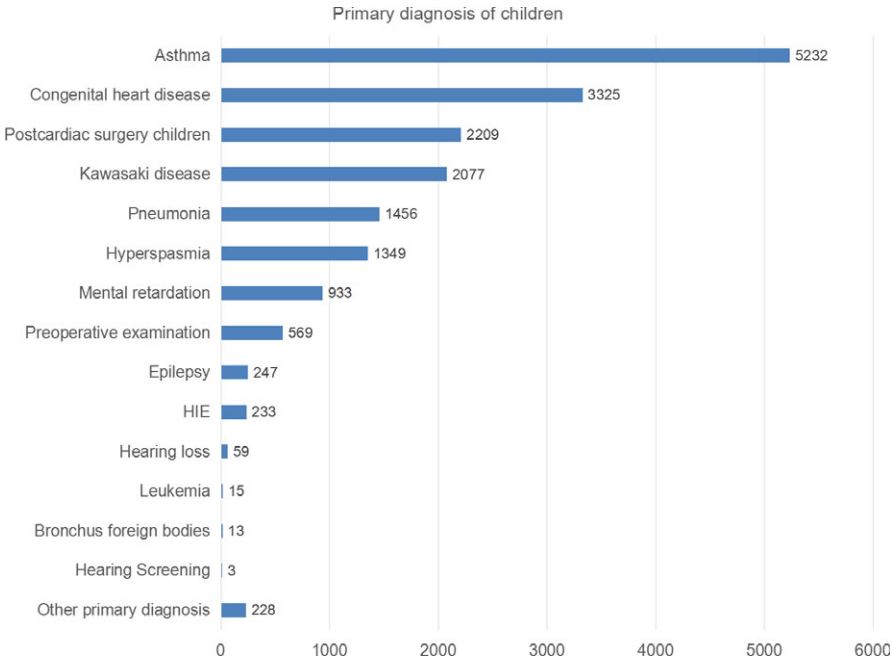

FIGURE 2 Primary diagnosis of children. Abbreviations: HIE, hypoxic ischemic encephalopathy [Colour figure can be viewed at wileyonlinelibrary.com]

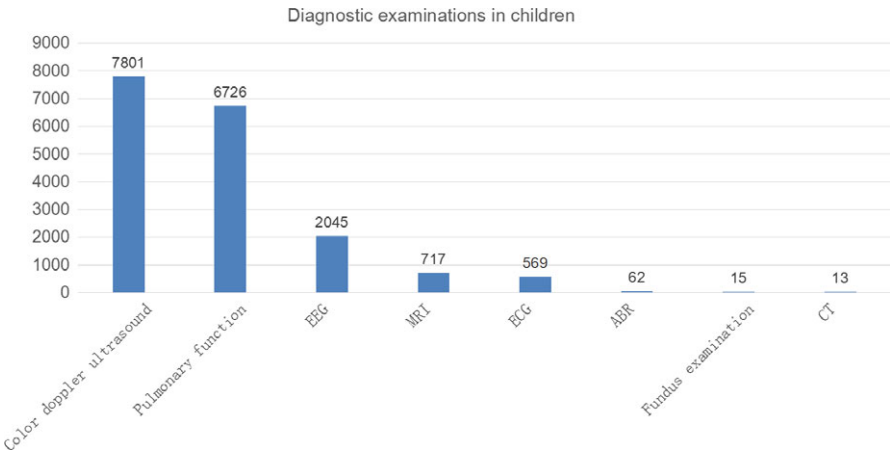

FIGURE 3 Diagnostic examinations in children. Abbreviations: ABR, auditory brain response testing; CT, computed tomography; ECG, electrocardiogram; EEG, electroencephalogram; MRI, magnetic resonance imaging [Colour figure can be viewed at wileyonlinelibrary.com]

3.5 | Minor adverse events

In total, minor adverse events occurred in 105 cases (0.59%; 95% CI: 0.48-0.71) (Table 3). These included 53 cases (0.3%) of PONV (95% CI: 0.22-0.39), 40 cases (0.22%) of reduced SpO_2 reduction (95% CI: 0.16-0.30), 20 cases (0.11%) of upper airway obstructions (95% CI: 0.07-0.17), 11 cases (0.07%) of delayed awakening (95% CI 0.03-0.12), 4 cases (0.02%) of unexpected changes in heart rate or blood pressure by >20% of the normal age-adjusted values and who required pharmacological interventions (95% CI: 0.21-0.37), and 3 cases (0.02%) of rash (95% CI: 0-0.05). PONV primarily occurred in children who underwent EEG examination.

TABLE 2 Major adverse events

Major adverse events	N (%)	95% CI
Emergent airway intervention	3 (0.02)	0-0.05
Cardiac arrhythmias	1 (0.01)	0-0.03
Laryngospasm	0 (0.00)	0-0.02
Cardiac arrest	0 (0.00)	0-0.02
Death	0 (0.00)	0-0.02

Variables expressed as numbers (%).

4 | DISCUSSION

This is a large-scale retrospective analysis of the rate of sedation success and adverse events associated with sedation using intranasal dexmedetomidine and ketamine among infants and children in a large tertiary hospital in China.

The sedation success rate of our analysis is similar or higher than those reported in previous studies,[9,10,17] and sedation time and onset time are shorter than other studies.[8,18] The reason behind this observation may be due to the combination therapy approach of dexmedetomidine and ketamine. Qiao found that the combination of

TABLE 3 Minor adverse events

Minor adverse events	N (%)	95% CI
PONV	53 (0.30)	0.22-0.39
SpO_2 reduction to <90% (for cyanotic congenital heart diseases, reduction by <10% of the baseline value)	40 (0.22)	0.16-0.30
Upper airway obstruction	20 (0.11)	0.07-0.17
Delayed awakening	11 (0.06)	0.03-0.11
Unexpected changes in heart rate or blood pressure by >20% normal, age-adjusted values, and given pharmacological intervention	4 (0.02)	0.01-0.06
Rash	3 (0.02)	0-0.05

Variables expressed as numbers (%).
Abbreviations: PONV, postoperative nausea and vomiting; SpO_2, blood oxygen saturation.

dexmedetomidine and ketamine was superior to either dexmedetomidine or ketamine when given alone.[19] Patients who required a second dose of intranasal medication with sedation failure were patients who underwent MRI examination, or had fever, cyanotic congenital heart disease, a history of congenital heart disease surgery, or a history of repeated sedation. The requirement for a second dose of medication was more likely to have a longer procedure. A recent report indicated that the median effective dose of intranasal dexmedetomidine for TTE after cardiac surgery was higher than that required for normal children.[20] The reason for this remains unclear. It could be envisaged that a high initial dose may improve the success rates of sedation but further research is needed to validate the safety and efficacy of high-dose intranasal sedation.

Our study found that the most minor adverse event was PONV (n = 53, 0.30%); All of the reported cases of PONV ceased with rest or injection of ondansetron (0.08 mg kg^{-1}). A number of studies reported PONV as the most common adverse effect of intranasal ketamine, with an incidence rate ranging from 4.7% to 35.3%.[1,19,21-25] The rate of PONV in our study is significantly lower than other reports. The reason may be related to the use of low-dose ketamine.

When defining adverse events related to this sedation regimen, we opted for the use of normal, age-adjusted values for better definition of predicted baseline mean arterial blood pressure and heart rate.[12,26,27] For our study, 7.3% (n = 1310) of children experienced an unexpected change in heart rate or blood pressure by >20% normal age-adjusted values. Our study are lower than those in previous studies of dexmedetomidine sedation.[9,10,28] This may be related to the combined use of ketamine. Some studies reported there was less hypotension when ketamine was added to dexmedetomidine.[19,29]

Numerous published studies found no adverse respiratory events associated with the use of intranasal dexmedetomidine and/or ketamine.[4,6-8,29] Rate of respiratory events observed in this study is similar. No laryngospasm and bronchospasm occurred. Our results thus echo the idea that intranasal sedation may be effective and safe in regards to minor adverse events.

This study has several limitations. First, due to the retrospective observational study design, certain data points should be interpreted with caution. For example, medical team members or parents may stimulate the patient, when the examination is complete, to awake the child from sedation, and the length of sedation may be affected by the extent of such stimulation. At the same time, time for onset of sedation and recovery time were both very crude estimates since nurses involved in the study did not constantly stimulate the patients in order to allow onset of sedation. Second, there could be selection bias, particularly with regards to the MRI study cases, due to the single-center study design. Third, the durations of the various diagnostic examinations were different when performed by different attending physicians. Patients were sent to the examination room once a satisfactory sedation effect was achieved but waiting times, evaluation times, and transfer times all varied, which could affect the success rate of sedation. The aforementioned limitations may have influenced the outcomes of the study and were unavoidable in this retrospective study. We anticipate that improved communications and transfer procedures between departments, the rate of successful sedation could be enhanced.

5 | CONCLUSIONS

Procedural sedation using a combination of dexmedetomidine and ketamine administered intranasally is associated with acceptable effectiveness and low rates of adverse events in a large cohort of children undergoing nonpainful procedures in our hospital. Further study data are warranted using a variety of dosage regimes in order to achieve satisfactory sedation for some patient subgroups as well as to explore the safety and efficacy profile of larger doses.

CONFLICT OF INTEREST

No conflicts of interest declared.

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